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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/396,985	09/15/1999	BRUCE A. BEUTLER	UTSD:602	8202

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EXAMINER	
BASI, NIRMAL SINGH	
ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/396,985	Applicant(s) BEUTLER ET AL
	Examiner Nirmal S. Basi	Art Unit 1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 29, 2002*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *38-40, 52-61, 63-68, 70-75, and 100-103* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *38-40, 52-61, 63-68, 70-75, and 100-103* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Amendment filed 9/30/02, paper number 21, has been entered. Declaration and Supplemental Response filed 10/29/02, paper number 22, has been entered.

Response To Applicants arguments

Claim Rejection, 35 U.S.C. 112, second paragraph

2. Claims 38-40, 52-61, 63-68, 70-75 and 100-103 remain rejected under 35 U.S.C. 112, second paragraph, for reason of record in paper number 14 (8/14/01) and 16 (4/23/02), as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 38, 40 and 52 remain indefinite because the name TLR-4 has not been defined in the claims and specification so as to allow the metes and bounds of the claims to be determined. Applicant argues TLR-4 has been defined to meet the requirements of 35 USC 112, second paragraph. Applicant argues the name TLR-4 is defined in the specification and is well known and defined in the literature. Applicant further argues, TLR-4 as used by the Applicant in describing a particular embodiment refers to polypeptides of sequences of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99 and those sequences at least about 85% similar thereto or biologically equivalent thereof. The Declaration of David D. Chaplin has been fully considered. Chaplin declares the application provides him with at least sufficient structural and functional properties by which to identify a protein as TLR-4 or its homolog. Further argued is that the structure of members of the TLR-4 family, and their function, primarily their role in mediating

responses to endotoxins, that identifies TLR-4 polypeptides. Applicants arguments and the Declaration of Chaplin have been fully considered but not found persuasive. The specification discloses, page 29, last paragraph to page 30, "the invention concerns isolated DNA segments and recombinant vectors incorporating DNA sequences that encode a TLR-4 protein or subunit that includes within its amino acid sequence a contiguous amino acid sequence in accordance with, or essentially as set forth in, SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99". Further stated is "The term "a sequence essentially as set forth in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99" means that the sequence substantially corresponds to a portion of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99 and has relatively few amino acids that are not identical to, or a biologically functional equivalent of, the amino acids of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99. The art nor specification disclose the structural and functional properties which must be present for the polypeptide to be classified as a TLR-4 polypeptide. There is no disclosure of the sequence of amino acids contained in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99.that are critical for function. There is no disclosure of which portions of the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99, when contained in a polypeptide would classify it as a TLR-4 polypeptide. The biological function corresponding to specific portion of the afore mentioned polypeptides is not disclosed. Chaplin discloses the function of TLR-4 proteins and their primary role in mediating responses to endotoxins identifies proteins as TLR-4 polypeptides. No disclosure is provided as to the sequence

of amino acids contained in polypeptide that is responsible for endotoxin signaling. The critical feature of the invention has not been disclosed. All proteins that mediate endotoxin response are not classified as TLR-4 polypeptides, absent evidence to the contrary. The name TLR-4 polypeptide encompasses, in view of the specification, modifications and changes which may be made to TLR-4 protein and subunits and still obtain a molecule having like or otherwise desirable characteristics ,see page 73. The structure associated with polypeptide encompassed by the name and the "like or otherwise desirable characteristics" are not disclosed so as to allow the metes and bounds of the claim to be determined. Applicants states on page 6, of paper number 11, filed 2/7/01, that the name has already been changed once from Toll-4 to TLR-4. Similarly other proteins may have different names, but encompass the same protein. Therefore without a clear disclosure of the structure and associated function of the TLR-4 protein the metes and bounds of the claim cannot be determined. Claims 38, 40, 52, 55, 56 and 63-64 remain indefinite because it is not clear what is a TLR-4. "TLR-4" is indefinite for reasons given above.

Claims 38, 40, 52 and 101-103 remain indefinite because it is not clear what is encompassed by "lipopolysaccharide mediated response", for reason of record in paper number 16, so as to allow the metes and bounds of the claim to be determined. Applicant argues the term lipopolysaccharide is a term synonymous with endotoxin and that the specification discloses a succinct description of the events and circumstances that comprise the initiation of a response to LPS and the resultant responses. The Declaration of Chaplin argues against the Examiners assertion that "lipopolysaccharide mediated response" is not clearly defined by stating, "I do not find this to be the

case". Chaplin further discloses that "the actors and elements of lipopolysaccharide mediated responses that are mediated by TLR-4" are disclosed in the specification. Chaplin further, provides examples, "TNF production and splenocyte proliferation assays, commonly employed assays for LPS response". Applicants arguments and the declaration of Chaplin have been fully considered but not found persuasive. Disclosing examples of the some of the "actors and elements of lipopolysaccharide mediated response", does not define which responses are considered mediated by lipopolysaccharide. The ambiguity of the "lipopolysaccharide mediated response" is highlighted by the specification, page 3, last paragraph, which states, "Thus, in spite of its importance, most of the endotoxin signaling pathway remains relatively unknown". Therefore, it follows, since term lipopolysaccharide is a term synonymous with endotoxin, and most of the lipopolysaccharide signaling pathway, i.e. "lipopolysaccharide mediated response" remains relatively unknown. Applicant states exemplary parameters and methods for measuring and determining the response are also found in several locations in the specification. Applicants arguments have been fully considered but not found persuasive. The specification does not provide a clear definition of the "lipopolysaccharide mediated response" and therefore the parameters used to determine the response can not be determined. The "lipopolysaccharide mediated response" and the parameters screened to determine the response are not defined so as to allow the metes and bounds of the claim to be determined. Where does the "lipopolysaccharide pathway" begin and end so the metes and bounds of the "lipopolysaccharide mediated response" can be determined?

New claims 101-103 remains indefinite because it is not clear what is a, "small molecule", so as to allow the metes and bounds of the claim to be determined. Applicant argues the meaning of the terms "small molecule inhibitor" is well established as referring to small molecules that inhibit whatever activity is involved in their application. Applicants arguments have been fully considered but not found persuasive. Applicant has not specifically addressed examiners rejection. The term "small molecule" in claims 101-103 is a relative term which renders the claim indefinite. The term "small molecule" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. When is molecule considered small as compared to when it is considered big so as to allow the metes and bounds of the claim to be determined. Also what is the boundary when a molecules transitions into a medium or big molecule?

Claims 39, 53-54, 57-61, 65, 66, 68, 70-75 are indefinite for depending on a base claim or intermediate claim and fail to resolve the issues raised above.

Claim Rejection, 35 U.S.C. 112, first paragraph

3. Claims 38-40, 52-61, 63-68, 70-75 and 100-103 remain rejected under 35 U.S.C. 112, first paragraph, for reasons of record in paper numbers 14 (8/14/8) and 16 (4/23/02), because the specification, while being enabling for a screening method for compounds which modulate a LPS mediated response by inducing the synthesis or altering expression of TLR-4 of SEQ ID NOs: 2, 4, 6, 98 and 99, does not reasonably provide enablement for other methods of screening for

compounds which may affect any other LPS-mediated responses or methods for identification of compounds which may predictably have other activities by any way other means than the altered expression of TLR-4 (SEQ ID NOs:2, 4, 6, 98 and 99). The, specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Applicants arguments have been fully considered but not found persuasive for the reasons given below.

Applicant argues TLR-4 is the key component of the signaling pathway that results, in, for example an increase TNF production as a result of lipopolysaccharide contact with cell surface receptors. Further Applicant and the Chaplin argue that the LPS response pathway can be used to assay for TLR-4 activity independently of any action upon TLR-4 expression. Applicant argues LPS response disclosed by the specification is by far not the sole means of modulating the TLR-4 response. Applicants arguments have ben considered but not found persuasive. Applicant states signaling in the TLR-4 pathway results for example in an increase in TNF production as a result of lipopolysaccharide contact with cell surface receptors. In the claimed method there is no disclosure of how the modulator targets a TLR-4 polypeptide and if the response being measured is in fact a lipopolysaccharide mediated response, since there is no controls to compare the results to. There is no contact of TL4-4 with a lipopolysaccharide. The same population of cells is being screened, all expressing TLR-4 polypeptide. The response may be due to some other pathway. For example cell death may be mediated by may different signaling pathways, it is not necessarily a lipopolysaccharide mediated response. Increase TNF production, if measured in instant method,

can be result of different signaling pathways, it is not necessarily a lipopolysaccharide mediated response. The method does not limit the modulator to target only the TLR-4 polypeptide in order to signal.

The claims are directed to screening for modulators of a LPS mediated response. The specification discloses that TLR-4 mRNA is induced by LPS (Fig 9) and TLR-4 is the limiting factor in LPS signal transduction in LPS responsive macrophages, the quantity of TLR-4 expressed is an important limiting factor in the intensity of the signal that is evoked (page 128). The specification discloses the screening of modulators of LPS mediated response where the compounds screened can modulate the expression of TLR-4 of SEQ ID NOs:2, 4, 6, 98 and 99. The scope of the claims which encompasses other methods of screening for modulators of LPS, using proteins other than those disclosed in SEQ ID NOs:2, 4, 6, 98 and 99, where the compounds may have activity by other means than the altered expression of TLR-4 expression of SEQ ID NOs:2, 4, 6, 98 and 99 is not enabled by the disclosure. For the person of ordinary skill in the art to screen for modulators of a LPS mediated response by any other means than those disclosed as "enabling" above, the artisan must first isolate other proteins capable of direct or indirect interaction with LPS and its modulators, and develop screening assays to determine if certain compounds can be modulators of the LPS mediated response. Therefore, the lack of guidance provided in the specification as to what other assays may be used to screen for modulators of LPS (see rejection under 112, second paragraph disclosing the difficulty in determining what is the scope of the lipopolysaccharide mediated

response), unpredictability and undue experimentation in isolating other TLR-4 polypeptides would prevent the skilled artisan from practicing the invention in its full scope.

4. No claim is allowed

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5. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO 10 **MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing** 15 **date of this final action.**

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner 20 should be directed to Nirmal Basi whose telephone number is (703) 308-9435. The examiner can normally be reached on Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for this Group is (703) 308-0294.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Nirmal S. Basi
Art Unit 1646
December 16, 2001

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